

A review of withdraw strategies for discontinuing antiepileptic therapy in epilepsy and pain management

Abstract

Purpose: Pain management is complicated by unacceptable levels of opioid abuse with few safe alternatives. The need exists for therapies of limited abuse potential and established pathways for their safe use. Antiepileptic drugs (AED) have been used as adjuncts to pain management since the 1960's. By virtue of their pharmacokinetic and adverse event (ADR) risk profiles, antiepileptic drugs require more prescriber surveillance compared to other medications. However, there is no published standard approach for discontinuing these drugs. The objectives of this review were to summarize the risk profile associated with tapering antiepileptic drugs used for epilepsy vs. AED use in pain management and to identify best practices for safe tapering.

Methods: A retrospective review of the literature was performed, addressing discontinuation of antiepileptic drugs. Articles were collected from PubMed and Ovid using keywords: anticonvulsant, antiepileptic, withholding treatment, taper and withdrawal. The limitations included English language only publications, regardless of country of origin, and publication between 1990 and 2013.

Results: A search of the literature revealed 25 published randomized controlled trials, reviews, case reports and editorials. While no taper guideline was found, many studies used a gradual taper protocol ranging from one month to more than four years for discontinuation; however there was no consistency between protocols. Adverse events for continuation and inappropriate discontinuation of antiepileptic therapy were aggregated from FDA labeled information and published case reports constituting the risk profile. The risk profile in acute AED discontinuation when used for epilepsy versus use in pain management, are very different. In epilepsy, documentation of acute discontinuation of AEDs reported recurrence of epileptic episodes. Tapering therapy to discontinuation in epilepsy resulted in a higher risk of seizure recurrence within the first six months of discontinuation compared to patients continuing therapy. When used as adjuncts to pain management, acute discontinuation of AEDs was reported as a benzodiazepine-like withdrawal syndrome with symptoms such as diaphoresis, agitation and altered mental status. However unlike true benzodiazepine withdrawal, acute discontinuation of AEDs in pain management was unresolved by benzodiazepine administration.

Conclusion: Tapering antiepileptic drugs when discontinuing therapy in epilepsy is common practice though there is no consistency amongst taper protocols documented in the literature. Tapering strategies for antiepileptic therapy when used in pain management are not well documented. This review identifies gaps in the literature concerning safe discontinuation of antiepileptic drugs when used in epilepsy as well as pain management. Further research is needed to establish safe tapering recommendations for AEDs which are specific to the applied use of the antiepileptic drug.

Keywords: antiepileptic drugs, withdrawal, tapering strategies, off-label use, pain management

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Introduction

Pain management is complicated by the levels of unacceptable opioid abuse and few safe alternatives. In 2011, the Institute of Medicine estimated 116million American adults suffered from chronic pain.¹ In 2008, the CDC reported drug-related death rates more than tripled since 1990 and opioid related deaths to be higher than that of heroin and cocaine combined.² Effective pain treatment options with limited abuse potential along with clear guidance on

safe and effective use are lacking in the pain management literature. Prescribers may utilize non-opioid analgesics along with adjunct therapies not indicated for pain to treat severe, persistent or chronic pain. Anti-epileptic drugs (AEDs) have been employed since the 1960's as adjunct pain management in both acute and chronic pain with the purpose of enhancing pain control and minimizing opioid exposure. In the primary indication of epilepsy, long-term use of AEDs is controversial and need only be used chronically in select patients.^{3,4} Evidence indicates cognitive side effects with long-term

use⁵ and literature demonstrates improvement with discontinuation^{5,6} yet a clear standard for how to safely discontinue AED therapy, was not found.

A 2012 AED off-label use study noted that 66.6% of all anticonvulsant prescriptions were prescribed for off-label indications. The study reported 99.2% off-label use of gabapentin, 99.5% of which was prescribed for neurogenic pain.⁷ An epidemiologic study of off-label AED use in the Georgia Medicaid population found phenytoin; valproate, gabapentin and carbamazepine to be the most commonly prescribed AEDs. Seventy-one point three percent of Georgia Medicaid patients with an AED prescription did not have an FDA-indicated diagnosis. AED use was strongly associated with concurrent pain management therapies however treatment indication was not available in the dataset.⁸ Given the high prevalence of off-label prescribing combined with the substantial but differential risks associated with use and acute discontinuation, there exists a need to establish clear and specific recommendations for discontinuing AED therapy. Without regard to applied use, there is substantial evidence of adverse events with acute withdrawal of AEDs⁹⁻¹⁴ however no currently published guidance address strategies to safely discontinue AED in either epilepsy or chronic pain management. The objectives of this paper are to summarize the risk profile of tapering antiepileptic drugs when used for epilepsy versus use as adjunctive therapy in pain management and to identify best practices for safe tapering.

Methods

Articles were identified by a search of PubMed and OVID databases, using keywords (anticonvulsant, antiepileptic, withholding treatment, taper and withdrawal) as well as a search of articles referenced by the retrieved publications. Date limitations for results took into consideration the long history of AED use but restricted to the time point at which off-label use manifested in the literature. Thus articles published between 1990 and 2013 were included in the analysis. No limitation was applied to country of publication however articles selected were restricted to the English language. Abstracts, prospective studies, reviews, editorials and case reports were included. A summary of the referenced articles were placed in a table with the headings source, title, author, intervention and findings.

Results

Anti-epileptics – adverse event risk profiles

The ADR profile for discontinuation of AEDs must balance the safety and toxicity concerns of continuing therapy in both the epileptic and pain management indications. The ADR profile for AED therapy varies depending upon the diagnosis to which AED therapy is utilized.

The long-term use risks of AEDs in epilepsy are well documented in the published literature and include cognitive impairments, behavioral changes and motor problems.¹⁵ Multiple AEDs used long-term in epilepsy have been associated with increased risk of memory decline, reduced attention and other cognitive impairments.⁵ By contrast, the long-term risks of AEDs used off-label for chronic pain have not been documented in the published literature.

In epilepsy, literature addressing taper of AED therapy notes an increased risk for seizure recurrence within the first 6 months of therapy discontinuation however beyond 6 months the risk of seizure recurrence was equal to therapy continuation.^{6,16-24} Where AEDs are utilized as adjuncts to pain management, acute discontinuation of

gabapentin results in a benzodiazepine-like withdrawal syndrome with symptoms of altered mental status, agitation,^{9,13} diaphoresis, nausea, insomnia, elevated blood pressure.^{12,14} The literature also includes a single report of status epilepticus in a patient with no previous history of epilepsy.⁹ Acute discontinuation of pregabalin was associated with benzodiazepine-like withdrawal symptoms of diaphoresis, elevated blood pressure, and unrest.¹⁰ All cases reported that administration of a benzodiazepine failed to resolve symptoms but resolution was achieved upon re-initiation of AED therapy.

Tapering anti-epileptics in epilepsy

Literature analysis revealed inconsistency among AED tapering methods utilized in epilepsy. The preponderance of AED literature focuses on the risk of relapse, the benefits of successful discontinuation, as well as patient characteristics that are prognostic for adverse events upon discontinuation. However, the literature offers no standard tapering protocols for discontinuing therapy in epilepsy. Table 1 is a summary of the reference articles.

The goal of AED therapy is to induce a remission, then discontinue the therapy when sustained remission is achieved.^{19,20} However, the literature indicates discontinuation decisions are made on a case by case basis and are predicated on individual patient characteristics rather than establish guidelines. A seizure-free interval of 2years or more was most commonly cited as the benchmark for considering discontinuation.^{17,21,23-26} Evaluation for discontinuation of therapy was based on risk factors associated with increased relapse rates. Predictors of potential recurrence cited were abnormal neurological evaluations, etiology of seizures, abnormal EEG findings at time of taper and family history^{3,4} though these characteristics were not unanimously accepted as risk factors.

The necessity of tapering AED in epilepsy was generally accepted though the literature was inconsistent regarding the time frame over which AED tapering should occur. The time frame for taper regimens ranged from 4weeks^{16,22,23} to 4years²³ for complete discontinuation. The first 6months after discontinuation of AEDs were associated with increased risk of seizure relapse though, beyond 6months relapse rates approached the level similar to that in patients continuing AED therapy.²² There were no standards for tapering AEDs amongst the collected studies (Table 1).

A Cochrane review examined rapid vs. slow taper schedules to assess safety and effectiveness of discontinuation time frames however only one article of weak methodology met criteria. The reviewing authors were unable draw conclusions about differences between tapering schedules (rapid vs slow taper).²⁷ A study by Ramos-Lizana and colleagues reported a trend towards higher relapse rates in the first 6 months for patients discontinued over a shorter period (4-6weeks v 4-6months). The relevance to taper is limited as the study purpose focused on differences in seizure recurrence between discontinuation and continuation groups not as a comparison of two tapering schedules.²²

Tapering anti-epileptics in pain management

The evidence for AED tapering when used in pain management is limited to case reports and tapering protocols were inconsistent amongst the reports. The case reports indicate that patients may experience withdrawal symptoms upon abrupt discontinuation after treatment periods as short as one month.¹³ Gabapentin was the drug most commonly reported as eliciting withdrawal symptoms (Table 2).

Case reports included withdrawal syndromes resulting from abrupt discontinuation of gabapentin^{9,13} or unsuccessful taper.^{12,14} Case reported tapers associated with pain management were significantly shorter (5-10days) than the weeks to months of tapering for epilepsy-related AED therapy. Given limited published evidence regarding taper of AEDs in pain management, overall safety and success cannot be determined. Specific to pain management, AEDs are typically used as adjunct therapy thus the effects on metabolism and pharmacodynamics of concomitant therapy must also be considered when discontinuing the AEDs however the literature identified for this review did not address these aspects of discontinuation.

Discussion

Antiepileptic drugs (AEDs) are commonly used off-label in non-epileptic patients for indications including bipolar disorder, neurogenic pain syndromes along with other diagnoses. In the case of pain management, AEDs are used as adjunct therapy which increases the potential for significant drug interactions. The influence of one drug's pharmacokinetics and pharmacodynamics upon other concomitant therapies should be considered as the dynamics of stable interacting drugs will change as their eventual absence may influence the effectiveness of taper or the need to adjust continuing therapies. This review of the literature examined best practices for tapering AEDs when utilized in seizure disorders in comparison to use in pain management therapy. There are no published recommendations for AED tapering when used in seizure disorders and little published experience with discontinuation of AEDs used in unlabeled indications. The ADR profiles for the individual agents relative to discontinuation of therapy are poorly documented though some published case reports exist.

This is in contrast to the neuropsychological and psychomotor side effects profiles with chronic use, which are well documented in the literature. Adverse event reporting specific to AED withdrawal syndrome continues to be reported however clear guidance for safe discontinuation of these agents has yet to be established. Egualé et al.⁷ noted in their 2012 epidemiology study, the estimated use of AEDs off-label is far more common than in government-approved indications⁷ indicating predominant use of AEDs off-label, where evidence for use and safe guidance may be weakest. In the absence of clear guidance and treatment goals in off-label indications, inadequate evidence on a safe discontinuation may relegate patients to indefinite AED therapy. Clinicians would benefit greatly from future research into strategies for safely tapering a patient off of AED therapy as well as enhance understanding of the effect AED discontinuation would have on remaining drug therapies.

Conclusion

Tapering antiepileptic drugs when utilized for epilepsy is common practice though no specific taper recommendations are found in the literature. Without regarding to diagnosis, the literature generally supports tapering as the safest method of AED discontinuation but reveals wide variation in AED tapering strategies employed for both on and off-label uses. This review demonstrates the need for additional study concerning safe discontinuation of antiepileptic drugs used both for epilepsy as well as pain management. Patient safety would benefit greatly from research into safe tapering strategies for discontinuing AED therapy as well as contributing additional insight to the impact AED discontinuation would have on the pharmacodynamics of other treatments the patient continues.

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Conflict of interest

Author declares that there is no conflict of interest.

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